Avanafil for the Treatment of men With Erectile Dysfunction: A Systematic Review and Meta-analysis of Randomized Controlled Trials

American Journal of Men's Health September-October 2019: 1–11 © The Author(s) 2019 Article reuse guidelines: sagepub.com/journals-permissions DOI: 10.1177/1557988319880764 journals.sagepub.com/home/jmh SAGE

Jinze Li, $MM^{1,*}$, Lei Peng, $MM^{1,*}$, Dehong Cao, $MD^{2,3,*}$, Lujia He, MD^4 , Yunxiang Li, MD^{1} , and Qiang Wei, MD^2

Abstract

Previous studies have reported the clinical efficacy of avanafil for erectile dysfunction (ED), but these findings are controversial. This study aims to investigate the safety and efficacy of avanafil for ED. EMBASE, PubMed, and Cochrane Library were searched extensively to obtain eligible studies. Clinical outcomes including successful vaginal penetration (SVP), successful intercourse (SI), International Index of Erectile Function-Erectile Function domain (IIEF-EF) score and treatment adverse events (TAEs) were compared using RevMan v.5.3. Eight RCTs involving 3,709 patients were included. The analysis demonstrated that compared with placebo, the SVP (RR = 3.20, 95% CI [2.60, 3.95], p < .001), SI (RR = 2.53, 95% CI [2.19, 2.92], p < .001), change in IIEF-EF score (MD = 4.57, 95% CI [3.68, 5.46], p < .001) and TAEs (RR = 1.78, 95% CI [1.38, 2.31], p < .0001) were significantly higher in the avanafil. In addition, avanafil 200 mg were higher than avanafil 100 mg in SI (RR = 0.86, 95% CI [0.75, 0.99], p = .03) and change in IIEF-EF score (MD = -1.34, 95% CI [-1.67, -1.01], p < .001), but there were no obvious differences in SVP (RR = 0.89; 95% CI [0.74, 1.08], p = .23) and TAEs (RR = 0.97, 95% CI [0.83, 1.14], p = .74) between the two doses. The present evidence suggests that avanafil (especially 200 mg) has the potential to be the drug of choice for ED, but more strict and larger sample size RCTs are need to validate the findings.

Keywords

Erectile dysfunction, avanafil, meta-analysis, randomized controlled trial

Received May 16, 2019; revised September 4, 2019; accepted September 16, 2019

Erectile dysfunction (ED) is defined as the inability of men to obtain or maintain enough erection to complete a satisfactory sexual activity (Hatzimouratidis et al., 2010). As a public health issue, ED has caused a serious negative psychological impact on patients and may affect the quality of life and the marital relationship of patients. The prevalence of ED increases with age, and it is necessary to find an effective and safe way to treat male ED (Laumann et al., 2005).

Oral phosphodiesterase type 5 inhibitors (PDE5-Is) are considered to be an effective method for the treatment of ED. Three of these drugs (such as sildenafil, vardenafil, and tadalafil) are recommended by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of ED (Bruzziches, Francomano, Gareri, Lenzi, & Aversa, 2013; Smith et al., 2013). In the ¹Department of Urology, Nanchong Central Hospital, The Second Clinical Medical College, North Sichuan Medical College, Nanchong, Sichuan, China

²Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China

³State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Collaborative Innovation Center for Biotherapy, Chengdu, China

⁴Department of Operation and Management, West China Hospital, Sichuan University, Chengdu, China

*These authors contributed equally to this work and should be considered as co-first authors.

Corresponding Author:

Yunxiang Li, Department of Urology, Nanchong Central Hospital, The Second Clinical Medical College, North Sichuan Medical College, No. 97 Renmin South Road, Shunqing District, Nanchong, Sichuan 637000, China. Email: liyunxinag369@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

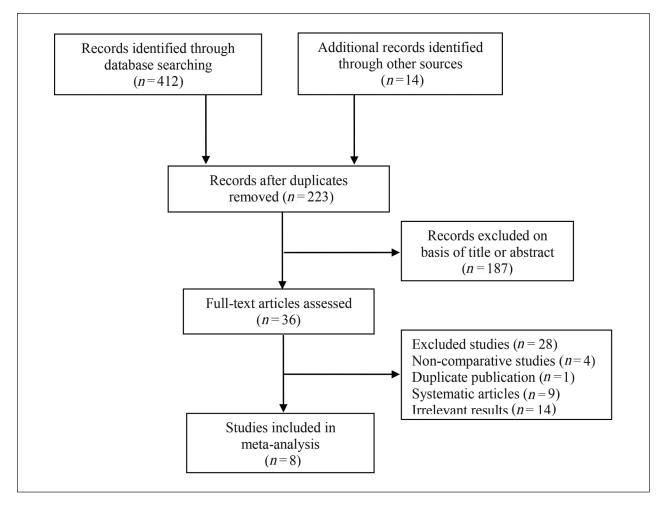


Figure 1. Flow diagram of bibliographic retrievals and results.

past 10 years, due to the occasional failure and adverse events, many patients are not satisfied with those drugs. As a new generation of PDE5-Is, avanafil is gradually accepted by patients due to its high selectivity and low adverse event response rate (Burke & Evans, 2012).

Although Wang performed a meta-analysis of the effectiveness of avanafil in the treatment of ED, the results are still controversial (Wang et al., 2014). The study was designed to include more relevant randomized controlled trials (RCTs) and analyze more parameters (such as the International Index of Erectile Function-Erectile Function domain [IIEF-EF] score) to assess the safety and efficacy of avanafil for the treatment of ED and provide updated clinical evidence.

Methods

Search Strategy

This study was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. As of April 2019, EMBASE, PubMed, and Cochrane Library were searched by the computer to distinguish all RCTs about the treatment of ED with avanafil. The search language was limited to English, and the following search terms were used: "avanafil," "erectile dysfunction," "randomized controlled trial." Besides, the author manually searched and applied Google scholarly literature to avoid the omission of studies.

Inclusion/Exclusion Criteria

If all correlative RCTs suffice the following criteria, they were included in the analysis: (a) all the studies on the therapy of ED with avanafil; (b) all patients were 18 years or older, and were clinically diagnosed with ED; (c) the control group in this study was either a placebo or a different dose of avanafil; (d) this study provided at least one indicator of outcomes that can be analyzed. On the contrary, studies were excluded if (a) the research data were based on the results of animal experiments; (b) the study data could not be obtained; or (c) all studies in non-RCTs. Figure 1 presents a flow chart of the study selection process.

Study	Country	Designs	LOE	Invention	Patients (n)	Age (years)	Dot (weeks)	Characteristics of the patient populations
Jung et al. (2010)	Korea	RCT	2b	A 100, 200 mg vs PL	8, 8 vs 6	$\begin{array}{c} 24.0 \pm 1.7, \\ 23.0 \pm 1.3 \\ \text{vs} \ 23.0 \pm 1.6 \end{array}$	2	 18–45 years, weighing >45 kg and within ± 20% of ideal body weight
Goldstein et al. (2012)	America	RCT	2b	A 100, 200 mg vs PL	157, 156 vs 155	56.4, 56.1 vs 55.8	12	≥18 years, type I or 2 diabetes, a ≥6-mo history of mild to severe ED
Goldstein et al. (2012)	America	RCT	2b	A 100, 200 mg vs PL	29, 3 vs 30	$\begin{array}{l} {\rm 58.2\pm9.6,}\\ {\rm 57.5\pm9.0}\\ {\rm vs58.2\pm8.6} \end{array}$	12	≥18 years, a ≥6-mo history of mild to severe ED
Zhao et al. (2012)	Korea	RCT	2b	A 100, 200 mg vs PL	68, 66 vs 66	$\begin{array}{c} {\rm 55.8\pm8.2,}\\ {\rm 56.6\pm8.3}\\ {\rm vs}\;{\rm 54.9\pm8.9} \end{array}$	12	>20 years, a ≥6-mo history of ED
Mulhall et al. (2013)	America	RCT	2b	A 100, 200 mg vs PL	99, 99 vs 100	$\begin{array}{l} 58.9\ \pm\ 5.9,\\ 57.7\ \pm\ 6.6\\ \text{vs}\ 58.6\ 5.9\end{array}$	12	 I8–70 years, a ≥6-mo history of ED after radical prostatectomy
Belkoff, Tursi, Uy, Smith , and Jones (2015)	America	RCT	2b	A 100, 200 mg vs PL	147, 147 vs 146	$\geq 8, \geq 8 \text{ vs}$ ≥ 8	8	≥18 years, a ≥6-mo history of mild to severe ED
Hellstrom et al. (2015)	America	RCT	2b	A 100, 200 mg vs PL	147, 200 vs 145	$\begin{array}{c} 58.5\ \pm\ 10.2,\\ 57.9\ \pm\ 10.6\\ \text{vs}\ 58.3\ \pm\\ 9.9\end{array}$	8	≥18 years, a ≥6-mo history of ED
Park et al. (2017)	Korea	RCT	2b	A 100, 200 mg vs PL	40, 39 vs 39	$\begin{array}{c} {\rm 57.2\pm8.0,}\\ {\rm 56.1\pm6.7}\\ {\rm vs56.7\pm9.0} \end{array}$	8	19–70 years, a ≥6-mo history of ED

Table I. Basic Information and Characteristics of Studies for Meta-Analysis.

Note. RCT = randomized controlled trial; LOE = level of evidence; A = avanafil; PL = placebo; vs = versus; Dot = duration of treatment; ED = erectile dysfunction; mo = month.

Data Extraction

After examining the title, abstract, and full text, two authors selected the literature in strict accordance with the inclusion criteria and then extracted the data according to the predesigned table for cross-checking. Differences can be dealt with by discussion. Data including first author, year of publication, type of study design, interventions, total number and age of subjects, characteristics of the patient populations, and outcome indicators were extracted. Data were collected independently by two investigators, and the missing data were acquired by contacting the author. The following outcomes data were extracted: successful vaginal penetration (SVP), successful intercourse (SI), change in IIEF-EF score, and treatment adverse events (TAEs). When continuous variables appeared in the studies in the form of the median (range), the mean values (standard deviation) was calculated by us (Luo, Wan, Liu, & Tong, 2018).

Quality Assessment

According to the new five-level evidence grading standard established by the Oxford Center for Evidence-Based Medicine (OCEBM), the level of evidence for all RCTs was 2b (Table 1). The quality assessment was based on methodological quality assessment criteria recommended by the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (Higgins et al., 2011). Where "high risk" stands for the high risk of bias, "low risk" stands for the low risk of bias and "unclear risk" stands for the absence of adequate information in the research to conduct the bias evaluation (Figure 2). All differences were resolved through discussions between the two commentators.

The funnel plot contributed a qualitative appraisal of the bias of published studies, and no evidence of bias was observed (Figure 3).

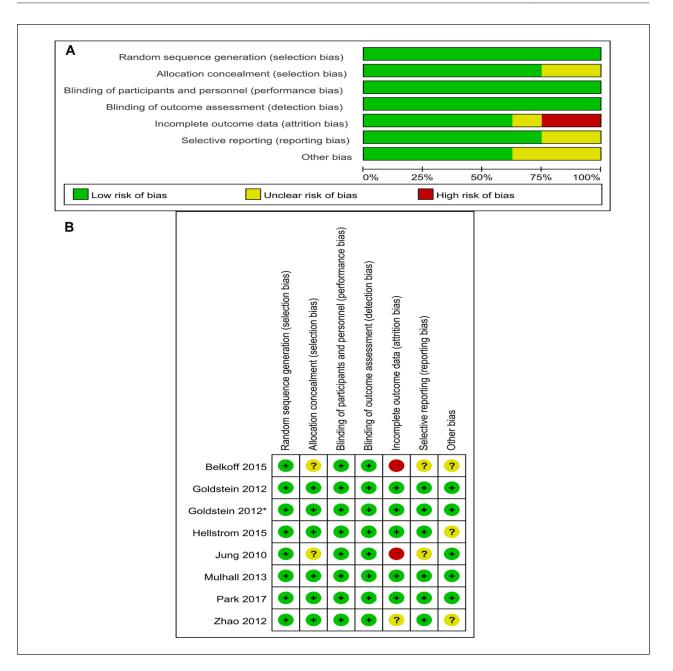


Figure 2. Quality of studies was assessed with the Cochrane Collaboration's tool (A: Risk of bias graph; B: Risk of bias summary).

Statistical Analysis

The RevMan 5.3 and Stata 14.0 were applied for data analysis. Mean difference (MD) and risk ratio (RR) were used as the effect indexes for continuous and dichotomous data respectively, and p value and 95% confidence interval (CI) were given for both. Heterogeneity between studies was judged by Cochran's Q and I² statistics. When there was statistical homogeneity between studies (p > .1, I² < 50%), a fixed-effects model was chosen for

meta-analysis. Otherwise, a random-effects model was utilized. About all statistical consequences, p < .05 was regarded as statistically significant.

Results

Study Characteristics

A total of 426 related literature were obtained by a preliminary examination. Three hundred and ninety

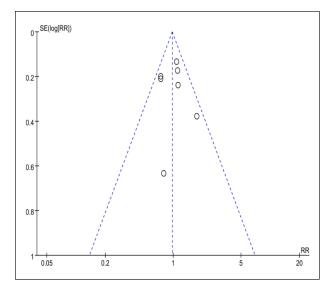


Figure 3. Funnel plot of the studies represented in the metaanalysis. RR = risk ratio; SE = standard error.

duplicate and unrelated studies were removed, and 36 studies were selected. After further reading the full text, eight RCTs (Belkoff, Tursi, Uy, Smith, & Jones, 2015; Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Hellstrom et al., 2015; Jung et al., 2010; Mulhall et al., 2013; Park et al., 2017; Zhao et al., 2012) involving 2,398 patients were included in the metaanalysis (Figure 1). In addition, the sample size was estimated according to the methodology introduced in the study (Belkoff et al., 2015), and some data were obtained from the Cochrane Central Register of Controlled Trials (Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Mulhall et al., 2013). The basic information and baseline characteristics of the incorporated studies are reported in Table 1, and the methodological quality evaluation of RCTs is presented in Figure 3.

Successful Vaginal Penetration

In the included studies, the data of SVP were reported in six RCTs involving 1,865 patients (Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Mulhall et al., 2013; Park et al., 2017; Zhao et al., 2012). The combined results displayed a significant improvement in SVP of patients in the avanafil group compared with the placebo group (RR = 3.20, 95% CI [2.60, 3.95], p < .001). In the study, a subgroup analysis of patients treated with 100 mg and 200 mg of avanafil for ED was performed. The pooled analysis demonstrated that compared to the placebo group, the 100 mg group had obvious statistical significance (RR = 3.02, 95% CI [2.24, 4.07], p < .001), and similar results were identified in the 200 mg group (RR = 3.39, 95% CI [2.60, 3.95], p < .001; Figure 4A).

5

Successful Intercourse

The SI data were extracted from seven RCTs (Belkoff et al., 2015; Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Hellstrom et al., 2015; Mulhall et al., 2013; Park et al., 2017; Zhao et al., 2012); the comprehensive analysis demonstrated that the proportion of SI in the avanafil group was significantly greater than that in the placebo group (RR = 2.53, 95% CI [2.19, 2.92], p < .001). The subgroup analysis results showed that both the avanafil 100 mg and 200 mg groups had significantly higher SI ratios than the placebo group (100 mg: RR = 2.36, 95% CI [2.21, 3.30], p < .001; Figure 4B).

IIEF-EF Score

Five RCTs recorded the change in IIEF-EF score data (Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Hellstrom et al., 2015; Mulhall et al., 2013; Park et al., 2017). Results indicated that the change in the IIEF-EF score of the avanafil group was significantly higher than that of the placebo group (MD = 4.57, 95% CI [3.68, 5.46], p < .001). In addition, similar results were found in the subgroup analysis. The MD was 3.88 (95% CI [2.69, 5.07], p < .001) for avanafil 100 mg group and 5.26 (95% CI [3.68, 5.46], p < .001) for avanafil 200 mg group (Figure 5A).

Treatment Adverse Events

In the final statistical analysis, seven RCTs reported the TAEs (Goldstein, Jones, et al., 2012; Goldstein, McCullough, et al., 2012; Hellstrom et al., 2015; Jung et al., 2010; Mulhall et al., 2013; Park et al., 2017; Zhao et al., 2012). The number of TAEs increased significantly in the avanafil group compared with the placebo group (RR = 1.78, 95% CI [1.38, 2.31], p < .0001; Figure 5B). The subgroup analysis suggested that the number of TAEs increased significantly in the placebo group (RR = 1.79, 95% CI [1.22, 2.62], p = .003). The same results were observed in the 200 mg group (RR = 1.81, 95% CI [1.22, 2.69], p = .003).

Avanafil 100 mg Versus Avanafil 200 mg

This analysis evaluated whether there were differences in efficacy and safety for ED treatment using either 100 mg or 200 mg avanafil (Figure 6). The pooled analysis revealed that avanafil 200 mg were higher than avanafil 100 mg in SI (RR = 0.86, 95% CI [0.75, 0.99], p = .03) and change in IIEF-EF score (MD = -1.34, 95% CI [-1.67, -1.01], p < .001), but there were no differences in SVP (RR = 0.89; 95% CI [0.74, 1.08], p = .27) and

Α	Avana		Placel			Risk Ratio				k Ratio	
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% C	l Year		M-H, Fix	xed, 95% Cl	
.1.1 Avanafil 100 mg			_								_
Goldstein 2012	27	126	8	127	7.9%	3.40 [1.61, 7.20]					
Zhao 2012	18	68	10	66	10.1%	1.75 [0.87, 3.50]					
Goldstein 2012*	42	157	11	155	11.0%	3.77 [2.02, 7.05]					
Mulhall 2013	29	94	10	96	9.9%	2.96 [1.53, 5.73]					
Hellstrom 2015	27	139	7	136	7.1%	3.77 [1.70, 8.37]			_		
Park 2017 Subtotal (95% CI)	9	40 624	4	39 619	4.0% 50.0%	2.19 [0.74, 6.54] 3.02 [2.24, 4.07]	2017				
· /	450	624	50	019	50.0%	3.02 [2.24, 4.07]				· ·	
Total events Heterogeneity: Chi² = 3	152	- (D - (50	00/							
Test for overall effect: 2				076							
1.1.2 Avanafil 200 mg											
Goldstein 2012*	45	156	11	155	11.0%	4.06 [2.19, 7.56]	2012				_
Goldstein 2012	28	126	8	127	7.9%	3.53 [1.67, 7.44]					_
Zhao 2012	19	66	10	66	10.0%	1.90 [0.96, 3.77]					
Mulhall 2013	37	96	7	96	7.0%	5.29 [2.48, 11.26]					
Hellstrom 2015	30	139	10	136	10.1%	2.94 [1.49, 5.77]					
Park 2017	11	39	4	39	4.0%	2.75 [0.96, 7.90]	2017				_
Subtotal (95% CI)		622		619	50.0%	3.39 [2.52, 4.55]				-	
Total events	170		50								
Heterogeneity: Chi ² = 4	.72, df = 5	5 (P = 0	0.45); I ² =	0%							
Test for overall effect: 2	Z = 8.11 (F	P < 0.0	0001)								
Total (95% CI)		1246		1238	100.0%	3.20 [2.60, 3.95]				•	
Total events	322		100								
Heterogeneity: Chi ² = 8	.57, df = 1	11 (P =	0.66); l ² :	= 0%							-+
								0.1	0.2 0.5	1 2 5	10
Test for overall effect: 2	2 = 10.87	(P < 0.)	00001)						Equation Averation	il Envoure Blassha	
Test for overall effect: Z Test for subgroup differ				(P = 0	.59), I² = 0	9%		I	Favours Avanafi	il Favours Placebo	
	ences: Cl	ni² = 0.:	29, df = 1		.59), I² = 0			I			
Test for subgroup differ	ences: Cl Avana	ni² = 0.: fil	29, df = 1 Placel	00		Risk Ratio M-H, Fixed, 95% C	l Year	I	Risl	il Favours Placebo k Ratio xed, 95% Cl	
Test for subgroup differ B	ences: Cl Avana	ni² = 0.: fil	29, df = 1 Placel	00		Risk Ratio	l Year		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup	ences: Cl Avana	ni² = 0.: fil	29, df = 1 Placel	00		Risk Ratio			Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg	ences: Cl Avana Events	ni² = 0.: fil <u>Total</u>	29, df = 1 Placet Events	oo Total	Weight	Risk Ratio M-H, Fixed, 95% C	2012		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012*	ences: Ch Avana Events 37 33 68	ni² = 0.: fil <u>Total</u> 68	29, df = 1 Placet Events 17	Total 66	Weight 8.4%	Risk Ratio <u>M-H, Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67]	2012 2012 2012		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhail 2013	rences: Ch Avana Events 37 33 68 26	fil Total 68 126 157 94	29, df = 1 Placet Events 17 14 22 14	66 127 155 96	Weight 8.4% 6.8% 10.8% 6.8%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40]	2012 2012 2012 2013		Risl	k Ratio	
Test for subgroup differ B <u>Study or Subgroup</u> 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015	rences: Cł Avana Events 37 33 68 26 41	fil Total 68 126 157 94 147	29, df = 1 Placel Events 17 14 22 14 20	66 127 155 96 146	Weight 8.4% 6.8% 10.8% 6.8% 9.8%	Risk Ratio <u>M-H, Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30]	2012 2012 2012 2013 2013		Risl	k Ratio	
Test for subgroup differ B <u>Study or Subgroup</u> 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015 Hellstrom 2015	rences: Cl Avana Events 37 33 68 26 41 20	fil Total 68 126 157 94 147 147	29, df = 1 Placet Events 17 14 22 14 20 3	66 127 155 96 146 145	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65]	2012 2012 2012 2013 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017	rences: Cł Avana Events 37 33 68 26 41	fil Total 68 126 157 94 147 147 40	29, df = 1 Placel Events 17 14 22 14 20	66 127 155 96 146 145 39	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5% 5.9%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62]	2012 2012 2012 2013 2013		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI)	rences: Cl Avana Events 37 33 68 26 41 20 18	fil Total 68 126 157 94 147 147	29, df = 1 Placel Events 17 14 22 14 20 3 12	66 127 155 96 146 145	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65]	2012 2012 2012 2013 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015 Heilstrom 2015 Park 2017 Subtotal (95% CI) Total events	rences: Cl Avana Events 37 33 68 26 41 20 18 243	hi ² = 0.: fil Total 68 126 157 94 147 147 147 40 779	29, df = 1 Placet Events 17 14 22 14 20 3 12 102	66 127 155 96 146 145 39 774	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5% 5.9%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62]	2012 2012 2012 2013 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7	rences: Cl Avana Events 37 33 68 26 41 20 18 243 3.95, df = 6	fil Total 68 126 157 94 147 147 40 779 6 (P = 0	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² =	66 127 155 96 146 145 39 774	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5% 5.9%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62]	2012 2012 2012 2013 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg	rences: Cl Avana Events 33 368 26 41 20 18 243 .95, df = 6 Z = 8.25 (f	$hi^2 = 0.1$ fil Total 68 126 157 94 147 147 40 779 6 (P = 0) 6 (P = 0)	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001)	66 127 155 96 146 145 39 774 25%	Weight 8.4% 6.8% 10.8% 6.8% 9.8% 1.5% 5.9% 50.1%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90]	2012 2012 2012 2013 2015 2015 2017		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup Study or Subgroup Table 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhall 2013 Beikoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 Z = 8.25 (F 37	fil fil Total 68 126 157 94 147 147 147 40 779 6 (P = 0) 6 < 0.00	29, df = 1 Placel Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17	500 Total 666 127 155 96 146 145 399 774 25% 66	Weight 8.4% 6.8% 10.8% 9.8% 1.5% 5.9% 50.1%	Risk Ratio <u>M-H. Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45]	2012 2012 2013 2015 2015 2017 2017		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012*	rences: Cf Avana Events 37 33 68 26 41 243 295, df = 6 2 = 8.25 (f 37 70	fil Total 68 126 157 94 147 147 40 779 6 (P = 0 P < 0.00 66 156	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22	500 Total 666 127 155 96 146 145 399 774 25% 66 155	Weight 8.4% 6.8% 9.8% 1.5% 5.9% 50.1% 8.3% 10.8%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83]	2012 2012 2013 2015 2015 2017 2017		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012* Mulhall 2013 Belkoff 2015 Heilstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012*	rences: Cf Avana Events 37 33 68 26 41 20 18 243 295, df = 6 Z = 8.25 (f 37 70 40	fil Total 68 126 157 94 147 147 40 779 6 (P = C) 66 156 126	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 22 14 20 3 12 102 102 102 102 102 102 102	66 127 155 96 146 145 39 774 25% 66 155 127	Weight 8.4% 6.8% 10.8% 9.8% 1.5% 5.9% 50.1% 8.3% 10.8% 6.8%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012 Mulhall 2013	Avana Avana 200 37 33 68 26 41 20 18 243 .95, df = 6 2< = 8.25 (f	fil = 0.3 $fil = 126$ 126 126 147 94 147 40 779 $6 (P = 0)$ 66 156 126 96	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 14 14 14 102 102 102 102 102 117 12 12 12 12 12 12 12 14 12 12 12 12 12 12 12 12 12 12	BOD Total 66 127 155 96 146 145 39 774 25% 66 155 127 96 145	Weight 8.4% 6.8% 10.8% 6.8% 1.5% 5.9% 50.1% 8.3% 10.8% 6.8%	Risk Ratio <u>M-H, Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2012		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012 Mulhail 2013 Hellstrom 2015	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 Z = 8.25 (f 37 70 40 36 25	fil Total 68 126 157 94 147 147 40 779 6 (P = 0 6 (P = 0 66 156 156 156 126 96 96 148	29, df = 1 Placet Events 17 14 22 14 20 3 12 0001) 102 0.24); I ² = 0001) 17 22 14 14 3 12 102 12 14 14 12 14 14 15 16 17 14 20 17 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 12 14 20 12 12 14 20 12 12 12 12 12 12 12 12 12 12	BOD 66 127 155 96 146 145 39 774 25% 66 155 127 96 145	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 1.5%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2013 2013 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Heilstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Hellstrom 2015 Belkoff 2015	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 Z = 8.25 (f 37 70 40 36 26 47	fil = 0.3 $fil = 126$ 126 157 94 147 147 40 779 $6 (P = 0)$ 66 156 126 96 148 147	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 14 20 3 12 102 1.24); l ² = 0001)	Control Control 66 127 155 96 146 145 399 774 25% 66 155 127 96 145 127 96 145 146	Weight 8.4% 6.8% 10.8% 9.8% 1.5% 50.1% 8.3% 10.8% 6.8% 6.8% 1.5% 9.8%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Heilstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2013 Hellstrom 2015 Belkoff 2015 Park 2017	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 Z = 8.25 (f 37 70 40 36 25	fil = 0.3 fil Total 68 126 157 94 147 40 779 6 (P = 0 5 < 0.00 66 156 126 96 148 147 39	29, df = 1 Placet Events 17 14 22 14 20 3 12 0001) 102 0.24); I ² = 0001) 17 22 14 14 3 12 102 12 14 14 12 14 14 15 16 17 14 20 17 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 14 20 12 12 14 20 12 12 14 20 12 12 12 12 12 12 12 12 12 12	Total 66 127 155 96 146 145 39 774 25% 66 155 127 96 145 145 145 39	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 5.9%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012 Mulhail 2013 Hellstrom 2015 Belkoff 2015 Park 2017 Subtotal (95% CI)	rences: Cf Avana Events 37 33 68 26 41 20 18 243 295, df = 6 Z = 8.25 (f 37 70 40 36 25 47 21	fil = 0.3 $fil = 126$ 126 157 94 147 147 40 779 $6 (P = 0)$ 66 156 126 96 148 147	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); I ² = 0001) 17 22 14 14 3 20 0.24); I ² = 0001)	Control Control 66 127 155 96 146 145 399 774 25% 66 155 127 96 145 127 96 145 146	Weight 8.4% 6.8% 10.8% 9.8% 1.5% 50.1% 8.3% 10.8% 6.8% 6.8% 1.5% 9.8%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup An an	rences: Cf Avana Events 37 33 68 86 26 41 20 18 243 295, df = 6 2 = 8.25 (f 37 70 40 36 25 47 21 276	$ \int \vec{r} = 0.; $ fil Total 68 126 157 94 147 147	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 3 20 0.24); l ² = 102 12 14 20 3 12 102 12 102 12 102 12 14 12 12 102 12 12 12 12 12 12 12 12 12 1	Do 66 127 155 96 145 39 774 25% 66 155 145 127 96 145 146 39 774	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 5.9%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B <u>Study or Subgroup</u> <u>1.3.1 Avanafil 100mg</u> Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012* Goldstein 2012 Goldstein 2015 Belkoff 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Subtotal (95% CI)	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 2 = 8.25 (f 37 70 40 36 25 47 21 276 6.57, df = 6	$ 1 ^2 = 0$ fil Total 68 126 157 94 147 147 147 147 147 6 (P = 0 6 (P = 0 6 (P = 0) 6 (P = 10) 126 126 126 126 126 126 126 126	29, df = 1 Placel Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 13 20 102 1.24); l ² = 102 102 122 14 12 102 122 14 12 102 122 14 12 12 12 12 12 12 12 12 12 12	Do 66 127 155 96 145 39 774 25% 66 155 145 127 96 145 146 39 774	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 5.9%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhail 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012 Mulhail 2013 Hellstrom 2015 Belkoff 2015 Park 2017 Subtotal (95% CI)	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 2 = 8.25 (f 37 70 40 36 25 47 21 276 6.57, df = 6	$ 1 ^2 = 0$ fil Total 68 126 157 94 147 147 147 147 147 6 (P = 0 6 (P = 0 6 (P = 0) 6 (P = 10) 126 126 126 126 126 126 126 126	29, df = 1 Placel Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 13 20 102 1.24); l ² = 102 102 122 14 12 102 122 14 12 102 122 14 12 12 12 12 12 12 12 12 12 12	Geo 66 127 155 96 146 145 374 25% 66 155 127 96 155 127 96 145 127 96 146 39 774 21%	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 5.9%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B Study or Subgroup 1.3.1 Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 Goldstein 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Goldstein 2013 Hellstrom 2015 Belkoff 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Total events Heterogeneity: Chi ² = 7 Total events	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 2 = 8.25 (f 37 70 40 36 25 47 21 276 6.57, df = 6	$P^2 = 0$ fil Total 68 126 157 94 147 40 779 6 (P = 0 66 156 126 96 126 96 126 96 126 96 126 96 126 96 126 96 126 96 126 126 126 126 127 147 147 147 147 147 147 147 14	29, df = 1 Placel Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 13 20 102 1.24); l ² = 102 102 122 14 12 102 122 14 12 102 122 14 12 12 12 12 12 12 12 12 12 12	Geo 66 127 155 96 146 145 374 25% 66 155 127 96 155 127 96 145 127 96 146 39 774 21%	Weight 8.4% 6.8% 10.8% 6.8% 1.5% 5.9% 50.1% 8.3% 10.8% 6.8% 6.8% 1.5% 9.8% 49.9%	Risk Ratio <u>M-H, Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04] 2.70 [2.21, 3.30]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risl	k Ratio	
Test for subgroup differ B <u>Study or Subgroup</u> <u>1.3.1 Avanafil 100mg</u> Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 1.3.2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012* Goldstein 2012 Goldstein 2015 Belkoff 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 Total (95% CI)	rences: Cf Avana Events 37 33 68 86 26 41 20 18 243 295, df = 6 2 = 8.25 (f 37 70 40 0 36 25 47 21 276 519	$P^2 = 0$ fil Total 68 126 157 94 147 40 779 6 (P = () 6 (P = () 6 (P = () 6 (P = () 779 8 (P = () 6 (P = () 779 147 147 40 779 6 (P = () 6 (P = () 157 147 147 147 147 147 147 147 14	29, df = 1 Placet Events 17 14 22 14 20 3 12 102 0.24); l ² = 0001) 17 22 14 102 0.24); l ² = 0001 12 102 0.227); l ² = 0001)	Total 66 127 155 96 146 145 39 774 25% 66 66 155 127 96 145 127 96 145 39 774 21%	Weight 8.4% 6.8% 10.8% 6.8% 1.5% 59.1% 50.1% 8.3% 10.8% 6.8% 1.5% 6.8% 1.5% 59.4% 9.8% 5.9% 49.9%	Risk Ratio <u>M-H, Fixed, 95% C</u> 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.82, 2.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04] 2.70 [2.21, 3.30]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risi	k Ratio xed, 95% CI	
Test for subgroup differ B Study or Subgroup Avanafil 100mg Zhao 2012 Goldstein 2012 Goldstein 2012 Goldstein 2012 Mulhall 2013 Belkoff 2015 Hellstrom 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 Avanafil 200mg Zhao 2012 Goldstein 2012* Goldstein 2012 Mulhall 2013 Hellstrom 2015 Belkoff 2015 Park 2017 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 Total events Heterogeneity: Chi ² = 7 Test for overall effect: 2 Total events	rences: Cf Avana Events 37 33 68 26 41 20 18 243 .95, df = 6 Z = 8.25 (f 37 70 40 36 25 47 21 276 55, df = 6 Z = 9.73 (f 9 6.26, df = 2 Z = 12.74	$ \vec{r} ^2 = 0.$ fil Total 68 126 157 94 147 147 147 147 779 δ (P = (66 156 126 96 148 148 147 39 778 δ (P = (C = 0.0) 66 (157 20 0 157 147 147 147 147 147 147 147 14	29, df = 1 Placel Events 17 14 22 14 20 3 12 102 0.24); I ² = 0001) 17 22 14 14 20 12 0001) 17 22 14 102 0001) 204; I ² = 0001) 204; I ² = 0001)	Do Total 66 127 155 39 774 25% 66 66 155 127 96 64 155 127 96 145 145 146 39 774 21% 1548 2 = 20%	Weight 8.4% 6.8% 10.8% 6.8% 5.9% 50.1% 8.3% 10.8% 6.8% 1.5% 6.8% 1.5% 6.8% 1.5% 6.8% 49.9%	Risk Ratio M-H, Fixed, 95% C 2.11 [1.33, 3.36] 2.38 [1.34, 4.22] 3.05 [1.99, 4.67] 1.90 [1.06, 3.40] 2.04 [1.26, 3.30] 6.58 [2.00, 21.65] 1.46 [0.0, 22, 1.62] 2.36 [1.93, 2.90] 2.18 [1.37, 3.45] 3.16 [2.07, 4.83] 2.88 [1.65, 5.02] 2.57 [1.49, 4.45] 8.16 [2.52, 26.45] 2.33 [1.46, 3.74] 1.75 [1.01, 3.04] 2.70 [2.21, 3.30] 2.53 [2.19, 2.92]	2012 2012 2013 2015 2015 2017 2017 2012 2012 2012 2012 2015 2015		Risi M-H, Fb	k Ratio	

Figure 4. Forest plot for the comparison of the avanafil (100 mg and 200 mg subgroup) and placebo group (A: SVP; B: SI). SVP = successful vaginal penetration. SI = successful intercourse.

TAEs (RR = 0.97, 95% CI [0.83, 1.14], p = .74) between the two doses.

Sensitivity Analysis

Sensitivity analysis was performed to determine the impact of each study data on the final outcomes. There were no significant differences in overall pooled RRs and MDs, regardless of which study was deleted (Figure 7).

Discussion

Although ED is a benign disease, it affects the patient's body and mental health and is closely related to the patient's quality of life, sexual relationship, and family stability (Laumann et al., 2005). The treatment of ED can only improve the degree of an erection and alleviate the pain of patients, but it cannot be completely cured. Avanafil is a new type of PDE5-Is. Compared with others, it has good pharmacodynamic and pharmacokinetic

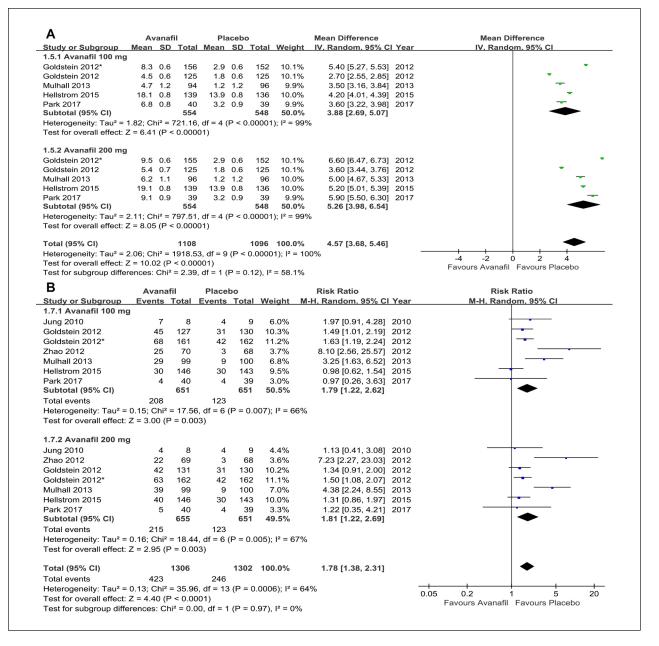


Figure 5. Forest plot for the comparison of the avanafil (100 mg and 200 mg subgroup) and placebo group (**A**: IIEF-EF score; **B**: TAEs). IIEF-EF = International Index of Erectile Function-Erectile Function domain; TAEs = treatment adverse events.

effects and has high selectivity for PDE5 isozyme, so there are fewer adverse reactions (Burke & Evans, 2012).

The present study showed that improvement of SVP in ED patients with avanafil at different doses (100 mg and 200 mg) was better than that in placebo patients, which was consistent with the analysis results of Wang et al. (2014) and Corona, Rastrelli, Burri, Jannini, and Maggi (2016). PDE5 is the major reactive enzyme for cGMP catabolism in cells and mediates the signal of erection disappearance. And the PDE5-Is (especially avanafil) are

analogs of the cGMP structure, they competitively bind to the catalytic group of PDE5 and inhibit the hydrolysis of cGMP, contributing to the increase of cGMP level, thereby increasing penile blood flow and amplifying the neural signal of erection (Andersson, 2003; Dean & Lue, 2005). It suggested that oral avanafil was an effective method for the treatment of ED. In addition, both Goldstein, McCullough, et al. (2012) and our study proved that there was no statistically significant difference in SVP between avanafil at 100 mg and 200 mg.

Α	Aug-51	100	Averativ	0.0		Bick Poti-	Risk Ratio
Study or Subaroup	Avanafil Events	100mg Total	Avanafil 2 Events		Woight	Risk Ratio M-H, Fixed, 95% CI Year	
Goldstein 2012*	<u>Events</u> 42	157	<u>Events</u> 45	156	26.5%	0.93 [0.65, 1.33] 2012	
Goldstein 2012	42	126	43 28	126	26.5% 16.5%	0.95 [0.65, 1.55] 2012	
Zhao 2012	18	68	20 19	66	11.3%	0.96 [0.60, 1.54] 2012	
Mulhall 2013	29	94	37	96	21.5%	0.80 [0.54, 1.19] 2013	
Hellstrom 2015	29	139	30	139	17.6%	0.90 [0.57, 1.43] 2015	
Park 2017	9	40	11	39	6.5%	0.80 [0.37, 1.43] 2013	
Total (95% CI)		624		622	100.0%	0.89 [0.74, 1.08]	•
Fotal events	152		170				
Heterogeneity: Chi ² = 0	0.54. df = 5	(P = 0.99)	$ 1^2 = 0\%$				
Test for overall effect:							0.2 0.5 1 2 5
	(.	,					Favours Avanafil 100mg Favours Avanafil 200mg
В	Avanafi	l 100 mg	Avanafi	200 mg		Risk Ratio	Risk Ratio
Study or Subgroup				0	al Weigh	nt M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Belkoff 2015	41				-		
Goldstein 2012	33						
Goldstein 2012*	68						_
Hellstrom 2015	19						
Mulhall 2013	26				6 12.79		_
Park 2017	20 17				9 8.09		
Zhao 2012	37	68	3 37	6	6 13.49	% 0.97 [0.72, 1.32]	
Total (95% CI)		779)	77	8 100.0	% 0.86 [0.75, 0.99]	\bullet
Total events	241		279				
Heterogeneity: Chi ² =	2.82, df = 6	6 (P = 0.83	3); $I^2 = 0\%$			_	
Test for overall effect:	Z = 2.17 (P = 0.03)					0.5 0.7 1 1.5 2 Favours Avanafil 100 mg Favours Avanafil 200 mg
С	Avanafil	100 mg	Avana	ïl 200 mg		Mean Difference	Mean Difference
Study or Subgroup	Mean	-	al Mean	-	a otal Weig		IV, Random, 95% Cl
Goldstein 2012		0.6 12			125 21.		- - -
Goldstein 2012*		0.6 15			155 21.		-
Hellstrom 2015		0.8 13			139 21.		- -
Mulhall 2013	4.7	1.2 94		1.1	96 18.		_ _
Park 2017	4.7 6.8	0.8 40		0.9	39 17.		
	0.0					. , ,	
Total (95% CI)	0 12: Chi2 -	554 - 52 52 df			554 100.	0% -1.34 [-1.67, -1.01]	
Heterogeneity: Tau ² = Test for overall effect:				0000T); P	- 92%		-2 -1 0 1 2
	z - 7.92 (P	< 0.00001	0				Favours Avanafil 100 mg Favours Avanafil 200 mg
D	Avanafil 1		Avanafil 2			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events		-	M-H, Fixed, 95% CI Year	M-H, Fixed, 95% Cl
Jung 2010	7	8	4	8	1.9%	1.75 [0.83, 3.67] 2010	
Goldstein 2012	45	127	42	131	19.3%	1.11 [0.78, 1.56] 2012	
Goldstein 2012*	68	161	63	162	29.3%	1.09 [0.83, 1.41] 2012	
Zhao 2012	25	70	22	69	10.3%	1.12 [0.70, 1.79] 2012	
Mulhall 2013	29	99	39	99	18.2%	0.74 [0.50, 1.10] 2013	
	30	146	40	146	18.7%	0.75 [0.50, 1.13] 2015	
	4	40	5	40	2.3%	0.80 [0.23, 2.76] 2017	
						0.07 [0.00.4.44]	
Park 2017 Total (95% Cl)		651		655	100.0%	0.97 [0.83, 1.14]	\mathbf{Y}
Hellstrom 2015 Park 2017 Total (95% CI) Total events	208	651	215	655	100.0%	0.97 [0.83, 1.14]	T
Park 2017 Total (95% Cl)	7.38, df = 6	(P = 0.29);		655	100.0%	0.97 [0.83, 1.14]	

Figure 6. Forest plot for the comparison of the 100 mg and 200 mg avanafil group (**A**: SVP; **B**: SI; **C**: IIEF-EF score; **D**: TAEs). SVP = successful vaginal penetration; SI = successful intercourse; IIEF-EF = International Index of Erectile Function-Erectile Function domain; TAEs = treatment adverse events.

Consequently, it is debatable whether high doses of avanafil have an advantage in improving SVP in ED patients.

This statistical analysis demonstrated that compared with placebo, avanafil (100 mg and 200 mg) significantly increased the proportion of SI in ED patients. A higher proportion of SI in patients receiving 200 mg of avanafil than in the lower-dose (100 mg) group. A previous metaanalysis incorporating four RCTs concluded that there was no difference in SI between the avanafil 100 mg and 200 mg groups (Cui, Li, Zong, Yan, & Zhang, 2014). There are a variety of reasons for this difference, for example, the study population's region, race, number, and age. Data from an epidemiological survey in China identified that higher prevalence of ED was observed in adult men with severe smoking, diabetes, and benign prostatic hyperplasia (Zhang, Yang, Li, & Li, 2017), and a recent study suggested that diabetic men with depressive symptoms may have a higher risk of developing ED (Wang, Yang, Cai, Wang, & Weng, 2018). These studies suggested that the treatment of ED patients may be affected by a combination of factors. The study conclusions are reasonable and warrant further objective evaluation of the impact of avanafil on improving SI at different doses (100 mg and 200 mg).

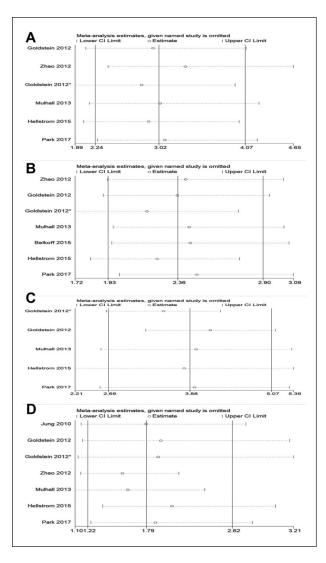


Figure 7. Sensitivity analysis. (**A:** sensitivity analysis of SVP; **B:** sensitivity analysis of SI; **C:** sensitivity analysis of IIEF-EF score; **D:** sensitivity analysis of TAEs). SVP = successful vaginal penetration; SI = successful intercourse; IIEF-EF = International Index of Erectile Function-Erectile Function domain; TAEs = treatment adverse events.

Since its introduction in 1997 (Rosen et al., 1997), the International Index of Erectile Function score (IIEF) has been widely accepted for its sensitivity and specificity in detecting changes in the treatment of ED patients. Hence, the IIEF-EF score has become one of the principal methods to estimate the quality of male ED. Our meta-analysis of change in IIEF-EF score demonstrated that different doses (100 mg or 200 mg) of avanafil were better than the placebo, which was consistent with the results of previous RCTs. Also, subgroup analyses indicated that higher doses (200 mg) of avanafil significantly increased change in IIEF-EF score in ED patients compared with avanafil 100 mg. There is no suspicion that avanafil can increase the IIEF-EF score significantly in patients with ED, and 200 mg of avanafil is better than 100 mg.

This meta-analysis showed a higher incidence of total TAEs in avanafil compared with placebo, and no difference was identified between avanafil 200 mg and 100 mg. According to the results of previous clinical trials, the total TAEs of avanafil were acceptable. In a 12-week phase III clinical study (Goldstein, McCullough, et al., 2012), the overall TAE rates for the avanafil 100 mg group, avanafil 200 mg group, and the placebo group were 42.9%, 38.9%, and 26.1%, respectively. The overall incidence of TAEs in patients receiving avanafil and placebo was 32.4% (423/1036) and 18.9% (246/1302), respectively. Further, the overall occurrence of TAEs was 18.2% (253/1389) and 22.5% (269/1197) in patients taking 100 mg and 200 mg avanafil, respectively. The most frequently reported adverse events included headache, flushing, nasal congestion, nasopharyngitis, and back pain (Belkoff et al., 2013; Goldstein, McCullough, et al., 2012; Hellstrom et al., 2012). It is gratifying to note that the extent of adverse events is relatively mild, patients can tolerate them, and there are few reports of serious complications in all studies.

Swearingen and his colleagues reported that compared with sildenafil, sublingual nitroglycerin had a lesser effect on blood pressure and heart rate after oral administration of avanafil for 1 h (p < .05); the adverse events associated with a clinically significant reduction in systolic blood pressure (\geq 30 mmHg) induced by avanafil were less common than sildenafil (15% vs 29%, p < .05; Swearingen, Nehra, Morelos, & Peterson, 2013). Another study also reported that avanafil is 120-fold and 10,000fold more selective for PDE5 than PDE6 and PDE1, while vardenafil is 21-fold and 1,000-fold and sildenafil is 16-fold and 380-fold (Kedia, Uckert, Assadi-Pour, Kuczyk, & Albrecht, 2013). There is a reason to believe that avanafil is a wise choice for patients who cannot tolerate TAEs to sildenafil and vardenafil.

There are certain limitations in the present analysis: (a) part of the study has a small sample size; (b) because the etiology of ED in some studies differs in the severity of ED and the expected response to the drug, the potential heterogeneity of the subjects used in the meta-analysis may be greater; (c) the follow-up period in the eight studies was shorter. Besides, most of the RCTs included did not explicitly describe allocation concealment.

Conclusion

The current evidence suggests that the SVP, SI, and IIEF-EF score in men who received avanafil improved significantly. Although some TAEs exist, they are within the tolerable range of patients. In summary, avanafil (especially 200 mg) has the potential to be the drug of

choice for the treatment of ED, but more strict and larger sample size RCTs are needed to verify the findings of this meta-analysis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Yunxiang Li D https://orcid.org/0000-0002-4019-7843

References

- Andersson, K. E. (2003). Erectile physiological and pathophysiological pathways involved in erectile dysfunction. *The Journal of Urology*, 170(2 Pt 2), S6–S13; discussion S13–14. doi:10.1097/01.ju.0000075362.08363.a4
- Belkoff, L. H., McCullough, A., Goldstein, I., Jones, L., Bowden, C. H., DiDonato, K., . . . Day, W. W. (2013). An open-label, long-term evaluation of the safety, efficacy and tolerability of avanafil in male patients with mild to severe erectile dysfunction. *International Journal of Clinical Practice*, 67(4), 333–341. doi:10.1111/ijcp.12065
- Belkoff, L. H., Tursi, J. P., Uy, J., Smith, T. M., & Jones, L. A. (2015). PD45-12 Avanafil efficacy within 15 minutes of dosing in men with mild to severe erectile dysfunction by demographic and baseline clinical characteristics. *The Journal of Urology*, 193(4s), e906. doi:10.1016/j. juro.2015.02.2584
- Bruzziches, R., Francomano, D., Gareri, P., Lenzi, A., & Aversa, A. (2013). An update on pharmacological treatment of erectile dysfunction with phosphodiesterase type 5 inhibitors. *Expert Opinion on Pharmacotherapy*, 14(10), 1333–1344. doi:10.1517/14656566.2013.799665
- Burke, R. M., & Evans, J. D. (2012). Avanafil for treatment of erectile dysfunction: Review of its potential. *Vascular Health and Risk Management*, 2012(8), 517–523. doi:10.2147/vhrm.S26712
- Corona, G., Rastrelli, G., Burri, A., Jannini, E. A., & Maggi, M. (2016). The safety and efficacy of Avanafil, a new 2(nd) generation PDE5i: Comprehensive review and meta-analysis. *Expert Opinion Drug Safety*, *15*(2), 237–247. doi:10.15 17/14740338.2016.1130126
- Cui, Y. S., Li, N., Zong, H. T., Yan, H. L., & Zhang, Y. (2014). Avanafil for male erectile dysfunction: A systematic review and meta-analysis. *Asian Journal of Andrology*, 16(3), 472–477. doi:10.4103/1008-682X.123670
- Dean, R. C., & Lue, T. F. (2005). Physiology of penile erection and pathophysiology of erectile dysfunction. Urologic Clinics of North America, 32(4), 379–395. doi:10.1016/j. ucl.2005.08.007
- Goldstein, I., Jones, L. A., Belkoff, L. H., Karlin, G. S., Bowden, C. H., Peterson, C. A., . . . Day, W. W. (2012). Avanafil for

the treatment of erectile dysfunction: A multicenter, randomized, double-blind study in men with diabetes mellitus. *Mayo Clinic Proceedings*, *87*(9), 843–852. doi:10.1016/j. mayocp.2012.06.016

- Goldstein, I., McCullough, A. R., Jones, L. A., Hellstrom, W. J., Bowden, C. H., Didonato, K., . . . Day, W. W. (2012). A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *The Journal of Sexual Medicine*, 9(4), 1122–1133. doi:10.1111/j.1743-6109.2011.02629.x
- Hatzimouratidis, K., Amar, E., Eardley, I., Giuliano, F., Hatzichristou, D., Montorsi, F., . . . Wespes, E. (2010). Guidelines on male sexual dysfunction: Erectile dysfunction and premature ejaculation. *European Urology*, 57(5), 804–814. doi:10.1016/j.eururo.2010.02.020
- Hellstrom, W. J., Freier, M. T., Serefoglu, E. C., Lewis, R. W., DiDonato, K., & Peterson, C. A. (2012). A phase II, singleblind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. *BJUInternational*, *111*(1), 137–147. doi:10.1111/j.1464-410X.2012.11267.x
- Hellstrom, W. J., Kaminetsky, J., Belkoff, L. H., Goldstein, I., Tursi, J. P., Uy, J., . . . Day, W. W. (2015). Efficacy of avanafil 15 minutes after dosing in men with erectile dysfunction: A randomized, double-blind, placebo controlled study. *The Journal of Urology*, 194(2), 485–492. doi:10.1016/j.juro.2014.12.101
- Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343, d5928. doi:10.1136/bmj.d5928
- Jung, J., Choi, S., Cho, S. H., Ghim, J. L., Hwang, A., Kim, U., . . . Lim, H. S. (2010). Tolerability and pharmacokinetics of avanafil, a phosphodiesterase type 5 inhibitor: A single- and multiple-dose, double-blind, randomized, placebo-controlled, dose-escalation study in healthy Korean male volunteers. *Clinical Therapeutics*, 32(6), 1178–1187. doi:10.1016/j.clinthera.2010.06.011
- Kedia, G. T., Uckert, S., Assadi-Pour, F., Kuczyk, M. A., & Albrecht, K. (2013). Avanafil for the treatment of erectile dysfunction: Initial data and clinical key properties. *Therapeutic Advances in Urology*, 5(1), 35–41. doi:10.1177/1756287212466282
- Laumann, E. O., Nicolosi, A., Glasser, D. B., Paik, A., Gingell, C., Moreira, E., & Wang, T. (2005). Sexual problems among women and men aged 40–80 y: Prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *International Journal of Impotence Research*, 17(1), 39–57. doi:10.1038/sj.ijir.3901250
- Luo, D., Wan, X., Liu, J., & Tong, T. (2018). Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Statistical Methods in Medical Research*, 27(6), 1785–1805. doi:10.1177/0962280216669183
- Mulhall, J. P., Burnett, A. L., Wang, R., McVary, K. T., Moul, J. W., Bowden, C. H., . . . Day, W. W. (2013). A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. *The Journal of Urology*, 189(6), 2229–2236. doi:10.1016/j.juro.2012.11.177

- Park, H. J., Kim, S. W., Kim, J. J., Lee, S. W., Paick, J. S., Ahn, T. Y., . . . Park, N. C. (2017). A randomized, placebo-controlled, double-blind, multi-center therapeutic confirmatory study to evaluate the safety and efficacy of avanafil in Korean patients with erectile dysfunction. *Journal of Korean Medical Science*, 32(6), 1016–1023. doi:10.3346/jkms.2017.32.6.1016
- Rosen, R. C., Riley, A., Wagner, G., Osterloh, I. H., Kirkpatrick, J., & Mishra, A. (1997). The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology*, 49(6), 822–830.
- Smith, W. B., II, McCaslin, I. R., Gokce, A., Mandava, S. H., Trost, L., & Hellstrom, W. J. (2013). PDE5 inhibitors: Considerations for preference and long-term adherence. *International Journal of Clinical Practice*, 67(8), 768–780. doi:10.1111/ijcp.12074
- Swearingen, D., Nehra, A., Morelos, S., & Peterson, C. A. (2013). Hemodynamic effect of avanafil and glyceryl trinitrate coadministration. *Drugs in Context*, 2013, 212248. doi:10.7573/dic.212248

- Wang, H., Yuan, J., Hu, X., Tao, K., Liu, J., & Hu, D. (2014). The effectiveness and safety of avanafil for erectile dysfunction: A systematic review and meta-analysis. *Current Medical Research and Opinion*, 30(8), 1565–1571. doi:10. 1185/03007995.2014.909391
- Wang, X., Yang, X., Cai, Y., Wang, S., & Weng, W. (2018). High prevalence of erectile dysfunction in diabetic men with depressive symptoms: A meta-analysis. *The Journal of Sexual Medicine*, 15(7), 935–941. doi:10.1016/j.jsxm.2018.05.007
- Zhang, X., Yang, B., Li, N., & Li, H. (2017). Prevalence and risk factors for erectile dysfunction in Chinese adult males. *The Journal of Sexual Medicine*, 14(10), 1201–1208. doi:10.1016/j.jsxm.2017.08.009
- Zhao, C., Kim, S. W., Yang, D. Y., Kim, J. J., Park, N. C., Lee, S. W., . . . Park, J. K. (2012). Efficacy and safety of avanafil for treating erectile dysfunction: Results of a multicentre, randomized, double-blind, placebo-controlled trial. *BJU International*, *110*(11), 1801–1806. doi:10.1111/ j.1464-410X.2012.11095.x